UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/524,516	02/11/2005	Hans Loibner	4518-0109PUS1	1154

2292 7590 04/10/2007
BIRCH STEWART KOLASCH & BIRCH
PO BOX 747
FALLS CHURCH, VA 22040-0747

EXAMINER	
SANG, HONG	
ART UNIT	PAPER NUMBER
1643	

SHORTENED STATUTORY PERIOD OF RESPONSE	NOTIFICATION DATE	DELIVERY MODE
3 MONTHS	04/10/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Notice of this Office communication was sent electronically on the above-indicated "Notification Date" and has a shortened statutory period for reply of 3 MONTHS from 04/10/2007.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mailroom@bskb.com

Office Action Summary	Application No.	Applicant(s)	
	10/524,516	LOIBNER ET AL.	
	Examiner	Art Unit	
	Hong Sang	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 February 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-23* is/are pending in the application.

4a) Of the above claim(s) *6 and 9-22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,7,8 and 23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *11 February 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/11/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

RE: Loibner et al.

1. Applicant's election with traverse of Group I (claims 1-8), EpCAM as antigen (a) and Lewis Y as antigen (b) in the reply filed on 2/5/07 is acknowledged. The traversal is on the ground(s) that no unity of invention objection was raised during international phase of this applicant, which also applies the unity of invention standard under PCT Rule 13, and an international applicant which complies with those unity of invention requirements must then be accepted by all of the designated and elected offices, including the USPTO, since Article 27(1) of the Patent Cooperation Treaty does not permit any national law or national office to require compliance with different regulations relating to the contents of the international application. The response states that an Examiner can properly make a restriction between different groups of claims but cannot properly restrict an applicant by dividing up the subject matter of a single claim and making a restriction within that claim. The response states that an Examiner may not, in this matter, refuse to make an examination on the merits of a broad generic claim.

Applicants' arguments have been carefully considered but are not found persuasive. As indicated in the previous office action, the instant application contains inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In accordance with 37 CFR 1.499, applicants are required to elect a single invention to which the claims must be restricted. While no unity of invention objections was raised during the international phase of this applicant, the search report did include several X references, which show that at least claims 1-5

are known in the art (see ISA search report). As indicated by these X references, the special technique feature that links the inventions or groups of inventions together is not novel and does not provide contribution over the prior art, therefore, unity of invention is lacking and the inventions are deemed to be separate. Regarding the restriction within a single claim, the MPEP states that "alternative forms of an invention may be claimed either in a plurality of independent claims, or in a single claim. In the latter case, the presence of the independent alternatives may not be immediately apparent. In either case, however, the same criteria should be applied in deciding whether there is unity of invention. Accordingly, lack of unity of invention may exist within a single claim. Where the claim contains distinct embodiments that are not linked by a single general inventive concept, the objection as to lack of unity of invention should be raised" (see MPEP 1850[R-5] II). PCT Rule 13.3 states "The determination whether a group of inventions is so linked as to form a single general inventive concept shall be made without regard to whether the inventions are claimed in separate claims or as alternatives within a single claim". In the instant case the special technique that links the inventions recited in the claims, i.e. different antibodies and different antigens are not novel and do not provide contribution over the prior art, therefore, the inventions in a single claim are deemed separate. Because of these reasons, the requirement is still deemed proper and is therefore made FINAL.

2. Applicants are reminded that election of (a) EpCAM and (b) Lewis y is a restriction requirement and not a species election.

3. The information disclosure statement (IDS) filed on 2/11/2005 has been considered. A signed copy is attached hereto.

4. Claims 1-23 are pending. New claim 23 is added. Claims 6, and 9-22 are withdrawn from further consideration as being drawn to non-elected inventions.

5. Claim 1-5, 7, 8 and 23 are under examination. Due to restriction/species election, claims are examined to the extent wherein antigen (a) is EpCAM and antigen (b) is Lewis Y.

Priority

6. Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

Claim Objections

7. Claims 1-5, 7, 8 and 23 are objected to because of the following informalities: claims contain non-elected inventions such as antibody, non-elected antigens NCAM, CEA, Lewis b, sialyl-Tn, and Globe H. Appropriate correction is required.

Claim Rejections - 35 USC § 112, 2nd paragraph

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 1-5, 7, 8 and 23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites the limitation "which set". There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 112, 1st paragraph

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claim 3 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in In re Wands, 8 USPQ2d 1400 (CA FC 1988). Wands states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention

Claim 3 is drawn to a kit for the combined use for the treatment of cancer patients, which kit comprises the following components: a) an antigen comprises at least one epitope of a cellular surface proteins and b) an antigen comprises at least one

epitope of an aberrant protein glycosylation, the kit is characterized in that the pharmaceutical preparation is formulated as a vaccine.

The invention is in a class of invention, which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The breadth of the claims

The standard meaning of the word "vaccine" recited in the claim is a preparation for preventing a disease. Therefore, the claim is drawn to a kit for treating and preventing a cancer.

Quantity of experimentation

The quantity of experimentation in this area is extremely large since there is no known drug in the art that is capable of preventing a cancer.

The unpredictability of the art and the state of the prior art

Claim recites the word "vaccine". The broadest reasonable interpretation of the claim in this situation is a kit for preventing a cancer.

No material has been found to date that has been shown to or would be expected to prevent cancer, and there is no working example, prior art, or any evidence that would provide the skilled artisan with any predictable guidance to use the claimed invention, it would be reasonable to conclude the claimed invention is not enabled.

Reasonable guidance with respect to preventing any cancer relies on quantitative analysis from defined populations that have been successfully pre-screened and are predisposed to particular types of cancer. This type of data might be derived from widespread genetic analysis, cancer clusters, or family histories. The essential element towards the validation of a preventive therapeutic is the ability to test the drug on subjects monitored in advance of clinical cancer and link those results with subsequent histological confirmation of the presence or absence of disease. This irrefutable link between antecedent drug and subsequent knowledge of the prevention of the disease is the essence of a valid preventive agent. Further, a preventive administration also must assume that the therapeutic will be safe and tolerable for anyone susceptible to the disease.

The art teaches that compositions comprising some tumor associated antigens are effective in treatment of cancer through generation of immunogenic response to the tumor antigen (see for example, Komenaka et al., Clinics in Dermatology, 2004, 22: 251-265, page 257). However, nowhere in the art does it show that tumor antigens are effective at preventing cancer. Rosenblatt et al. (Expert Opin. Biol. Ther., 2005, 5(5): 703-715) teach that "Animal models have demonstrated that DCs can be manipulated to express tumor antigens. Vaccination with DC-based vaccines results in the induction of antitumor cellular immune responses, protection against tumor challenge and, in some models, the eradication of established disease. These studies establish important biological principles regarding the nature of tumor immunology and the capacity to overcome tumor-associated tolerance through effective presentation of tumor antigens.

However, their applicant to the human setting is complicated by a myriad of factors. The relationship between host immunity and spontaneously established tumors in cancer patient is far more complex than that observed in animal models in which immunogenic tumors are artificially introduced. To be effective in the clinical realm, DC vaccines must be optimized with regard to antigen presentation and costimulation, migration to sites of interaction with reactive T cell population, recruitment of endogenous immune mechanisms, intensity and durability of the antitumor response, and preventing tumor escape and immune suppression" (see page 709, right column, 3rd paragraph). Evans *et al* (Q. J. Med 1999: 92: 299-307) teach that vaccines against cancer are not fully established, and it is stated that adjuvant therapy to prevent or delay disease still needs experimentation. Evans *et al* further state that such cancer vaccines are at best used as a therapeutic and not as a prophylactic and that *"the notion that cancer vaccines will replace standard therapeutic strategies in malignant disease still belongs to the realm of fiction"* (see page 303 last paragraph).

Heretofore the art has only recognized the treatment of a cancer.

Working examples

The specification teaches determination of the EpCAM expression, the Lewis Y expression and the EpCAM and Lewis Y co-expression on tissue samples of breast cancer (see page 22, lines 13-14, page 23, lines 11-12, and page 24, lines 14-15). The specification teaches active immunization of rhesus monkeys with a vaccine based on a He2-Lweis Y neoglycoprotein and further determination of the titers of anti-EpCAM and anti-Lewis Y antibodies (see page 25, lines 17-18). The specification teaches

determination of disseminated tumor cells from peripheral blood (see page 26, lines 4-5). The specification teaches combinatorial targeting of tumor cells related protein and oligosaccharide antigens in SKBR3 cell lines using anti-Her2-neu (Herceptin) and anti Ly-Y(IGN311) antibodies and further determination of antibody dependent cellular cytotoxicity (see Example 2, page 27). The specification teaches that combination of IGN311 and Herceptin leads to an enhanced lysis potential, greater than the effect that would have been observed by the sum of the individual components (page 31, 2nd paragraph). The specification teaches selection of an EpCAM-Lewis Y neoepitope specific antibody (see page 31, Example 3).

Guidance in the specification

The specification provides insufficient guidance and objective evidence to indicate to one of skill in the art that the administration of the pharmaceutical composition comprising an antigen comprising at least one epitope of EpCAM and an antigen comprising at least one epitope of Lewis Y would be enabling to prevent cancer.

Level of skill in the art

The level of skill in the art is deemed to be high.

Conclusion

Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of the art, the large quantity of research required to define these

unpredictable variables, the lack of guidance provided in the specification, the presence of a working example which does not address the issue of preventing a cancer using the claimed composition and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Claim Rejections - 35 USC § 102

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

13. Claims 1-3, 5, 7, and 8 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 01/35989A2 (Pub. Date: 5/25/2001, IDS) (English translation CA 2391927).

WO 01/35989A2 teaches that within an immunologic meaning, some anti-idiotypic antibodies can represent the "internal image" of an antigen, such antibodies may therefore be used, as a vaccine, for inducing an immune response in cancer patients, said immune response being possibly directed against said tumor-associated antigen (see page 2, 3rd paragraph and page 3, lines 3-6 of CA 2391927). WO 01/35989A2 teaches a pharmaceutical composition (vaccine) comprising anti-idiotypic antibody for EpCAM, anti-idiotypic antibody for Lewis Y, or anti-idiotypic antibodies for both EpCAM and Lewis Y antigens obtained from monkey serum by immunoaffinity

purification with a monoclonal antibody for EP-CAM, a monoclonal antibody for Lewis Y antigen, or monoclonal antibodies for both EpCAM and Lewis Y (see page 7, Examples 1-7, and claim 16).

Because the specification teaches that anti-idiotype antibodies are considered as antigens, i.e. are an embodiment of the invention (see page 17, 4th paragraph), therefore, the anti-idiotype antibodies of EpCAM and Lewis Y taught by WO 01/35989 A2 anticipate the claimed antigens.

Claim Rejections - 35 USC § 103

14. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

15. Claims 1-5, 7, 8 and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 01/35989A2 (Pub. Date: 5/25/2001, IDS) (English translation CA 2391927) in view of Maruyama et al. (Cancer Immunol Immunother., 2000, 49: 123-132), Sabbatini et al. (Int. J. Cancer, 2000, 87: 79-85), and Berthelsen et al. (US Patent No. 6,455,290B1, Date of Patent 9/24/2002, effective filing date 7/9/1999).

The teachings of WO 01/35989A2 are set forth above as they applied to claims 1-3, 5, 7 and 8 (see paragraph 13 above)

WO 01/35989A2 does not teach the vaccine that is formulated as an intravenously tolerable product. WO 01/35989A2 does not teach the antigen (a) is

EpCAM and antigen (b) is Lewis Y. However, these efficiencies are made up for in the teachings of Bertheslen, Maruyama and Sabbatini et al.

Bertheslen et al. disclose that the method of making intravenously tolerable preparation comprising antibodies or polypeptides are known in the art (see column 20, lines 45-61).

Maruyama et al. teach that the immunomodulatory activity of the native antigen GA733 (EpCAM) is superior to that of the anti-idiotypic antibody (Ab2) which mimicking a single EpCAM epitope (see abstract).

Sabbatini et al. teach vaccine comprising Lewis y antigen for treating ovarian cancer (see abstract)

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, and one would have been motivated to make the vaccine of WO 01/35989A2 as an intravenously tolerable product because intravenous administration of a vaccine comprising an antibody or polypeptide has been known and well practiced in the art, and has advantages in that the vaccine can be quickly delivered to tumor site at higher concentration. One of ordinary skill in the art would have a reasonable expectation of success to make the vaccine of WO 01/35989A2 as an intravenously tolerable product because the method of preparing a vaccine comprising an antibody or polypeptide for intravenous administration is known is the art as shown by Berthelsen et al.

Moreover, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to make a vaccine comprising the native EpCAM

and Lewis Y antigens in view of the teachings of WO 01/35989A2, Maruyama and Sabbatini et al. One would have been motivated to do so because Maruyama et al. teach that the native tumor antigen is superior to the anti-idiotypic antibody. One of ordinary skill in the art would have a reasonable expectation of success to do so because WO 01/35989A2 teaches a vaccine comprising anti-idiotypic antibodies of EpCAM and Lewis Y for treating cancer, Maruyama and Sabbatini et al. teach a method of treating cancer using a native tumor antigen EpCAM and Lewis y, respectively.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made.

16. Claims 1-5, 7, 8 and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Spitler (US Patent NO. 5,738,867, 4/14/1998) in view of Sabbatini et al. (Int. J. Cancer, 2000, 87: 79-85), and Berthelsen et al. (US Patent No. 6,455,290B1, Date of Patent 9/24/2002, effective filing date 7/9/1999).

Spitler teaches an antitumor vaccine composition comprising a GS-733-2 antigen (EpCAM) in a liposomal carrier (see abstract and claim 1) for treatment of cancer including ovary cancer (see column 2, lines 24-27). Spitler teaches that the antitumor vaccine further contains an additional synthetically prepared tumor associated antigen (see claim 2). Spitler teaches that the antitumor vaccine compounds may be employed in cocktails of two or more different TAAs encapsulated in and/or conjugated to liposomes, and such cocktails may be of particular in certain highly metastatic cancers (see the paragraph bridging columns 4 and 5)

Sabbatini et al. teach vaccine comprising Lewis y antigen for treating ovarian cancer (see abstract).

Bertheslen et al. disclose that the method of making intravenously tolerable preparation comprising antibodies or polypeptides are known in the art (see column 20, lines 45-61).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to make a vaccine comprising EpCAM and Lewis Y antigens in view of the teachings of Spitler, and Sabbatini et al. One would have been motivated to do so because Spitler et al. teach that the vaccine comprising EpCAM antigen can be used for treating ovary cancer, and can further comprise additional tumor associated antigen, Sabbatini et al. teach that vaccine comprising Lewis y antigen can be used for treating ovarian cancer, and because it is known in the art that using two cancer drugs often results in synergistic effects. "It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art." In re Kerkhoven, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980). One of ordinary skill in the art would have a reasonable expectation of success to do so because Spitler teaches a method of making a vaccine comprising EpCAM and Sabbatini et al. teach a method of making a vaccine comprising Lewis y.

Moreover, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, and one would have been motivated to make the vaccine as an intravenously tolerable product because intravenous administration of a vaccine comprising an antibody or polypeptide has been known and well practiced in the art, and has advantages in that the vaccine can be quickly delivered to tumor site at higher concentration. One of ordinary skill in the art would have a reasonable expectation of success to make the vaccine as an intravenously tolerable product because the method of preparing a vaccine comprising an antibody or polypeptide for intravenous administration is known is the art as shown by Berthelsen et al.

Conclusion

17. No claims are allowed.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Hong Sang whose telephone number is (571) 272 8145. The examiner can normally be reached on 8:30am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry R. Helms can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only.

For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Hong Sang, Ph.D.
Art Unit 1643
March 26, 2007

CHRISTOPHER H. YAEN
PRIMARY EXAMINER